



PATENTS

Attorney Docket Number 102286.123

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Turski *et al.*
Serial No.: 09/746,662
Filing Date: December 22, 2000
Title: **Treatment of Demyelinating Disorders**

Art Unit: 1646
Examiner: Ruixiang Li

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CERTIFICATION UNDER 37 CFR § 1.8(a)

I hereby certify that this correspondence is being deposited with the United States Postal Service as First Class Mail in an envelope addressed Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

September 5, 2003
Date of Signature and
of Mail Deposit

Maureen DiVito
Maureen DiVito

DECLARATION OF TERENCE SMITH UNDER 37 C.F.R. § 1.132

Dear Sir:

I, Terence Smith declare as follows:

1. I currently hold the position of Head of Pharmacology at Eisai London Research Laboratories Ltd., which is the assignee of the above-referenced patent application ("the Application"). I have worked, initially performing and latterly supervising research in the field of multiple sclerosis, particularly animal models of the disease, since obtaining my PhD in Pharmacology in 1992. My professional experience, educational background, professional activities, and publications are detailed in the



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curriculum vitae attached hereto as Exhibit A. In addition, similar details are included for the co-inventor, Prof. Dr. Lechoslaw Turski, attached hereto as Exhibit B.

2. As one of the inventors, I have personal knowledge of the invention disclosed and claimed in the Application.

3. It has been brought to my attention that in the Final Office Action mailed on March 6, 2003, the Examiner rejected claims 21-22 and 24-25 of the Application under 35 U.S.C. § 103(a) as allegedly being obvious over Shishikura et al., U.S. Patent No. 6,133,258 ("Shishikura") in view of Csuzdi et al., WO 97/28163 ("Csuzdi"), and rejected claims 23, 29-30, and 38 under 35 U.S.C. § 103(a) as allegedly being obvious over Shishikura in view of Csuzdi and further in view of Prineas et al., "Demyelinating Diseases," in Greenfield's Neuropathology, 813-896 (1997) ("Prineas").

4. I have reviewed the cited references, and my understanding of their teachings is set out below.

5. Before I set out my detailed understanding of the prior art documents, it is necessary to consider the definitions of the terms "neurodegenerative disorders" and "demyelinating disorders" as accepted by the medical and scientific community. Neurodegenerative disorders encompass diseases and conditions of the brain or other parts of the nervous system which result from the progressive death of neurons and loss of function. Examples of such neurodegenerative disorders include Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS or motor neuron disease), Huntington's disease, stroke and traumatic brain injury. Whilst there are few therapies available for neurodegenerative disease, ionotropic glutamate receptor antagonists, (including AMPA receptor antagonists) represents an attractive target for such conditions (as indicated in Csuzdi and Shishikura). In contrast, demyelinating disorders are diseases and conditions in which the myelin sheath of nerves of the peripheral or central nervous system is destroyed. Examples of such demyelinating disorders include multiple sclerosis, acute disseminated encephalomyelitis, acute demyelinating polyneuropathy (Guillain-Barre syndrome), chronic inflammatory



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demyelinating polyneuropathy, Marchifava-Bignami disease, central pontine myelinolysis, Devic syndrome, Balo disease, HIV- and HTLV- myelopathy, and progressive multifocal leucoencephalopathy. Prior to the work carried out by Eisai and included in this application, treatments for these conditions were limited, the clinical mainstay being steroids.

6. Prior to the work carried out by Eisai there was no teaching in the art that the glutamate ionotropic AMPA receptor was a target for the treatment of demyelinating disorders. The innovative endeavours of the co-inventors, Prof. Dr. Lechoslaw Turski and myself resulted in the discovery of an interaction between the AMPA receptor and paralysis seen in an accepted model of a demyelinating disease. This work (as claimed in the present application) was reported in Nature Medicine 2000, 6:62-66. The novelty of this discovery is highlighted by its inclusion in the News and Views section of the Nature Medicine (see Nature Medicine 6:15-16), which has an impact factor of 28.5, ranked 5th of all published scientific journals.

7. None of the prior references disclose the interaction of the AMPA receptor with a demyelinating disorder nor that AMPA antagonists interfere with the process of demyelination.

8. The prior references will now be considered in more detail.

9. Shishikura discloses certain AMPA receptor antagonists as useful for treating neurodegenerative disease. There is no discussion in Shishikura of the treatment of the class of demyelinating disorders, and no suggestion that an AMPA receptor antagonist could be used to treat demyelinating disorders. Thus, Shishikura does not suggest the use of an AMPA receptor inhibitor for treating any disorder induced by demyelination. There is no teaching of any link between demyelination and any disease states. Instead, Shishikura simply teaches a narrow class of compounds (neuroprotecting agents) for use in preventing the destruction of neurons.



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10. Csuzdi teaches 2,3-benzodiazepine derivatives and their use as noncompetitive AMPA receptor inhibitors for treating neurological disorders. However, Csuzdi does not discuss demyelinating disorders or suggest that the disclosed 2,3-benzodiazepine derivatives could be used to treat demyelinating disorders. Instead, Csuzdi merely teaches that 2,3-benzodiazepine derivatives can be used to prevent the destruction of neurons.

11. One of ordinary skill in the field of neurology reading Shishikura in combination with Csuzdi would be taught that AMPA receptor inhibitors, such as 2,3-benzodiazepine derivatives, can be used to treat neurodegenerative disorders. However, neither reference suggests that demyelinating disorders can be treated with AMPA receptor antagonists.

12. Prineas discloses the pathological features of various demyelinating disorders. However, Prineas does not suggest the treatment of demyelinating disorders with inhibitors of the interaction of glutamate with the AMPA receptor complex.

13. Thus, the combination of cited references does not teach or suggest the treatment of demyelinating disorders by administering an inhibitor of the interaction of glutamate with the AMPA receptor complex, alone or in combination with another agent. It is submitted that the Examiner is considering this invention with the benefit of hindsight. The teachings that the treatment of demyelinating disorders can be achieved by administering an inhibitor of the interaction of glutamate with the AMPA receptor complex are only related now because of the invention as set out in the present application, underlining the inventiveness of the present application.

14. Furthermore, prior to the Application, one of ordinary skill in the field of neurology would have had no motivation to combine the teachings of the cited references, because they are directed to distinct subject areas. Specifically, there would have been no motivation to combine the teachings of Shishikura and Csuzdi, which relate to agents for treating neurodegenerative diseases, with the teachings of Prineas, which relate to demyelinating diseases.



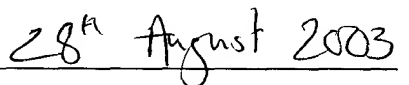
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I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed:


Terence Smith

Dated:



CURRICULUM VITAE: TERENCE SMITH

DATE OF BIRTH: 13th October 1964 **NATIONALITY:** British

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ADDRESS (work): Eisai London Research Laboratories Limited
 Bernard Katz Building, University College London
 Gower Street, London, WC1E 6BT UK
 Telephone: 0044 (0)20 7413 1145
 e-mail: Terence_Smith@eisai.net

CURRENT EMPLOYMENT*August 1997 – present:*

Head of Pharmacology, Eisai London Research Laboratories, London.

In 1992 the London laboratories of Eisai, a leading Japanese pharmaceutical company, were established at UCL with the specific aim of developing novel therapies for CNS degenerative disease. I joined the company in 1997 to expand the portfolio of *in vivo* models of CNS disease. Under my guidance, models of the human demyelinating disease, multiple sclerosis (MS), were established and utilised in the drug screening process. During the past four years, a drug finding project, germinating from the exchange of ideas between London and Tsukuba (Japan), has flourished and now involves a score of researchers including chemists, cell biologists and pharmacologists. The fruition of this work was published in Nature Medicine (January 2000) and Phase I clinical studies were successfully completed September 2002. Phase IIa studies are currently on-going (completion anticipated Autumn 2003).

PREVIOUS EMPLOYMENT*October 1991 – July 1997:*

Post Doctoral Research Scientist, Multiple Sclerosis Laboratory, Institute of Neurology, 1 Wakefield Street, London WC1N 1PJ.

October 1990 - September 1991

Research Assistant. Department of Medicine, Charing Cross and Westminster Medical School, St. Dunstan's Road, Hammersmith, London, W6 8RP.

October 1987 - September 1990

Ph.D Student (MRC Funded). Department of Pharmacology, Charing Cross and Westminster Medical School, St. Dunstan's Road, Hammersmith, London, W6 8RP.

August 1985 - July 1986

Sandwich Student. Applied Physiology Division, Institute of Naval Medicine, Alverstoke, Hampshire. Lung function laboratory operator; thermal and exercise physiology studies on naval ratings.

ACADEMIC QUALIFICATIONS*January 1992:* Ph.D. Faculty of Science, University of London

Thesis entitled "The Influence of Glucocorticoids on the Expression of Lipocortins 1,2 and 5 in the Brain and Pituitary Gland of the Rat

July 1987: B.Sc. Honours Degree in Applied Biological Sciences (Upper Second Class)
University of the West of England (formerly Bristol Polytechnic)*1983* Four 'A' Levels*1978* Eight 'O' Levels

INVITED TALKS

Open University, 5 May 2003, Milton Keynes, UK.

Symposium: Relevance of cell death in development and disease of the brain. Charité Hospital, Humboldt University 24-25 February 2003, Berlin, Germany.

Cambridge University Department of Neurology, 10 December 2002, Cambridge, UK.

3rd European School of Neuroimmunology, 11-14 September 2002, Tampere, Finland.

British Inflammation Research Association 3-4 July 2002, Bath, UK.

Euroglia 21-25 May 2002, Rome, Italy.

PUBLICATIONS

Groom A.J., **Smith T.**, Turski L. (2003). Multiple sclerosis and glutamate. *Ann N Y Acad Sci.* 993:229-75; discussion 287-8.

Ohgoh M., Hanada T., **Smith T.**, Hashimoto T., Ueno M., Yamanishi Y., Watanabe M. and Nishizawa Y. (2002). Altered expression of glutamate transporters in experimental autoimmune encephalomyelitis. *J. Neuroimmunol.* 125: 170-178.

Banati R.B., Newcombe J., Gunn R.N., Cagnin A., Turkheimer F., Heppner F., Price G., Wegner F., Giovannoni G., Miller D.H., Perkin G.D., **Smith T.**, Hewson A.K., Bydder G., Kreutzberg G.W., Jones T., Cuzner M.L. and Myers R. (2000). The peripheral benzodiazepine binding site in the brain in multiple sclerosis: quantitative in vivo imaging of microglia as a measure of disease activity. *Brain* 123:2321-2337.

Smith T., Groom A., Zhu B. and Turski L. (2000). Autoimmune encephalomyelitis ameliorated by AMPA antagonists. *Nature Medicine* 6: 62-66.

Folcik V.A., **Smith T.**, O'Bryant S., Kawczak J.A., Zhu B., Sakuri H., Kajiwar A., Staddon J.M., Glabinski A., Chernosky A.L., Tani M., Johnson J.M., Tuohy V.K., Rubin L.L. and Ransohoff R.M. (1999). Treatment with BBB022A or rolipram stabilizes the blood-brain barrier in experimental autoimmune encephalomyelitis: an additional mechanism for the therapeutic effect of type IV phosphodiesterase inhibitors. *J. Neuroimmunol.* 97: 119-128.

Smith T., Hewson A.K., Kingsley C.I., Leonard J.P. and Cuzner M.L. (1997). Interleukin-12 induces relapses in experimental allergic encephalomyelitis in the Lewis rat. *Am. J. Pathol.* 150: 1909-1917.

Leonard J.P., Waldburger K.E., Schaub R.G., **Smith T.**, Hewson A.K., Cuzner M.L. and Goldman S.J. (1997). Regulation of the inflammatory response in animal models of multiple sclerosis by interleukin-12. *Crit. Rev. Immunol.* 17: 545-553.

Smith T., Schmeid M., Hewson A.K., Lassmann H. and Cuzner M.L. (1996). Apoptosis of T-cells and macrophages in the central nervous system of intact and adrenalectomised Lewis rats during experimental allergic encephalomyelitis. *J. Autoimmun.* 9: 167-174.

Storch M.K., Fischer-Colbrie R., **Smith T.**, Rinner W.A., Hickey W.F., Cuzner M.L., Winkler H and Lassmann H. (1996). Co-localization of secretoneurin immunoreactivity and macrophage infiltration in the lesions of experimental autoimmune encephalomyelitis. *Neuroscience* 71:885-893.

Hewson A.K., **Smith T.** and Cuzner, M.L. (1995). Suppression of experimental allergic encephalomyelitis in the Lewis rat by the matrix metalloprotease inhibitor Ro31-9790. *Inflamm. Res.* 44:345-349.

Smith S.F., Benjamin J., Dewar A., Sheppard M., Fox B., **Smith T.**, Guz A. and Tetley T.D. (1995). Effect of dexamethasone on carrageenin-induced inflammation in the lung. *Med. Inflamm.* 4: 273-281.

Smith S.F., Tetley T.D., Datta A.K., **Smith T.**, Guz A. and Flower R.J. (1995). Lipocortin-1 distribution in bronchoalveolar lavage from healthy human lung: effect of prednisolone. *J. Appl. Physiol.* 79: 121-128.

Smith T., Hewson A.K., Quarrie L., Leonard J.P. and Cuzner M.L. (1994). Hypothalamic PGE₂ and cAMP production and adrenocortical activation following intra-peritoneal endotoxin injection: *in vivo* microdialysis studies in Lewis and Fischer rats. *Neuroendocrinol.* 59: 396-405.

Smith T. and Cuzner M.L. (1994). Neuroendocrine-immune interactions in homeostasis and autoimmunity. *Neuropathol. Appl. Neurobiol.* 20: 413-422.

Smith T., Flower R.J. and Buckingham J.C. (1993). Lipocortins 1,2 and 5 in the central nervous system and pituitary gland of the rat: selective induction by dexamethasone of lipocortin 1 in the anterior pituitary gland. *Mol. Neuropharmacol.* 3: 45-55.

Invited book chapters

Smith T. and Hewson A.K. (1997). Neuroendocrine-induced immune modulation and autoimmunity. In the *Handbook of Immune Modulating Agents*. Editor Kresina, T.F. pp 363-383. Marcell Dekker Inc. NY.

Cuzner M.L. and **Smith T.** (1995). Immune responses in the central nervous system in inflammatory demyelinating disease: in *Immune Responses in the Nervous System. The Molecular and Cellular Neurobiology Series*. Editor Rothwell, N.J. pp 117-142. Bios Scientific Publishers.

Buckingham J.C., **Smith T.** and Loxley H.D. (1991). The control of ACTH Secretion: in *The Adrenal Gland* (second edition). *Comprehensive Endocrinology* (revised series). Editor James, V.H.T. pp. 131-158. London: Raven Press.

CURRICULUM VITAE

Name: Prof. Dr. med. LA Turski MD

Date and place of birth: August 10, 1955, Opole-Lubelskie, Poland

Marital status: Married to Prof. Dr. med. C Ikonomidou, MD
(Greek/German) since October 12, 1985

Nationality: German

Children: Christopher Andreas Turski (December 3, 1986)
Gabrielle Nicole Turski (April 25, 1990)
Jennifer Sabrina Turski (June 22, 2000)

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Home address: Prof. Dr. med. L. Turski
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Education:

Primary school
1961-1969: Primary school No. 2 in Opole-Lubelskie, Poland

Secondary school
1969-1972: Adam-Mickiewicz Gymnasium in Opole-Lubelskie, Poland

Graduate school
1972-1978: Lublin Medical School, Poland

1980: MD Lublin Medical School, Poland
Thesis title: Central action of kainic acid in rats

1988: PhD Georg-August-University Göttingen, Germany
Thesis title: The convulsant action of pilocarpine in rats: Pharmacological, electroencephalographic and morphological analysis of the role of cholinergic mechanisms in epileptogenesis

Clinical training:

1978-1981: Resident, Internal Medicine, Department of Internal Medicine, Lublin Medical School, Poland

Management training:

1997: University of Michigan Business School, Ann Arbor, MI, USA

Licensure and certifications:

1978: Polish Medical Licence
 1993: German Medical Licence (22.09.1993)
 1994: German Board of Pharmacology and Toxicology
 1997: German Board of Clinical Pharmacology

Positions held:

1978-1981: Resident in Pharmacology and Toxicology at the Institute of Clinical Pathology, Department of Pharmacology, Lublin Medical School, Poland
 1978-1981: Resident in Internal Medicine at the Institute of Internal Medicine, Department of Gastroenterology, Lublin Medical School, Poland
 1981-1983: Postdoctoral Fellow with K Kuschinsky MD, Department of Biochemical Pharmacology, Max-Planck-Institute for Experimental Medicine, Göttingen, Germany
 1983-1984: Postdoctoral Fellow with K-H Sontag PhD, Max-Planck-Institute for Experimental Medicine, Göttingen, Germany
 1984: Postdoctoral Fellow with BS Meldrum MD, Department of Neurology, Institute of Psychiatry, University of London, London SE5 8AF, UK
 1985-1987: Assistant Professor, Max-Planck-Institute for Experimental Medicine, Göttingen, Germany
 1984-1988: Assistant Professor of Pharmacology, Department of Pharmacology, Institute of Clinical Pathology, Lublin Medical School, Poland
 1988-1993: Associate Professor of Neuropharmacology, Department of Pharmacology and Toxicology, Georg-August-University, Göttingen, Germany
 1993- Professor of Pharmacology, Department of Pharmacology and Toxicology, Georg-August-University, Göttingen, Germany
 1987-1997: Head of Experimental Neurology, Research

1997-1999:	Laboratories of Schering AG, Berlin, Germany Director of Pharmacology, University College London,
1999-2001:	Eisai London Research Laboratories, London, UK Head of Research, Solvay Pharmaceuticals bv, Weesp, The Netherlands
2001-	Vice President Global Discovery, Solvay Pharmaceuticals bv, Weesp, The Netherlands and Solvay Pharmaceuticals GmbH, Hannover, Germany

Fellowships and scholarships:

1. Fellowship - European Training Programme in Brain and Behaviour Research - France (Strasbourg) - 1981
2. Fellowship - Max-Planck-Society Fellowship for Visiting Scientists, 1981-1983

Memberships in professional societies:

German Society of Pharmacology and Toxicology
International Basal Ganglia Society
Society for Neuroscience

Honors and awards:

1972	Scapula aurea awarded by the Lublin Medical School
1977	Award of the Student Scientific Association, Poznan Medical School, Poland
1978	Award of the Student Scientific Association, Katowice, Silesian Medical School, Poland
1983	Award of the Minister of Health and Public Care for Research Achievements, Warsaw, Poland (1st Prize)
1984	1st Prize of the Polish Academy of Sciences, Warsaw, Poland
1985-1986	Michael Prize for Epilepsy Research, Jerusalem, Israel

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1. Rechberger T, Turski L, Turski W, Wojcik E (1979) The influence of atropine on the antiamphetamine action of fluphenazine. *Ann Univ M Curie-Sklodowska (Lublin) Sectio D* 34: 333-339
2. Kleinrok Z, Czuczwar SJ, Turski L (1980) Prevention of kainic acid-induced seizure-like activity by antiepileptic drugs. *Pol J Pharmacol Pharm* 32: 261-264
3. Kleinrok Z, Czuczwar SJ, Turski L, Zarkowski A (1980) Effect of intracerebroventricular injection of kainic acid on electrically and chemically induced convulsions in mice. *Pol J Pharmacol Pharm* 32: 265-269
4. Kleinrok Z, Turski L, Wawrzyniak M, Cybulska R (1980) The locomotor and exploratory activities in rats after lesion of hippocampal pyramidal cells with kainic acid. *Pol J Pharmacol Pharm* 32: 625-637
5. Kleinrok Z, Turski L (1980) Kainic acid-induced wet dog shakes in rats. The relation to central neurotransmitters. *Naunyn-Schmiedeberg's Arch Pharmacol* 314: 37-46
6. Turski L, Kleinrok Z (1980) Effects of kainic acid on body temperature of rats. Role of catecholaminergic and serotonergic systems. *Psychopharmacology* 71: 35-39
7. Turski L, Turski W, Czuczwar SJ, Kleinrok Z (1981) Effects of morphine and nalorphine on kainic acid-induced hypothermia in rats. *Psychopharmacology* 72: 211-214
8. Czuczwar SJ, Turski L, Kleinrok Z (1981) Atropine reversal of kainic acid-induced decrease in the leptaol convulsive threshold. *J Pharm Pharmacol* 33: 44-45
9. Kleinrok Z, Turski L, Wawrzyniak M, Cybulska R (1981) The locomotor and stereotypy response to dopaminergic drugs and caffeine after intracerebroventricular kainic acid in rats. *Pol J Pharmacol Pharm* 33: 149-159
10. Kleinrok Z, Turski L (1981) Biochemical consequences of kainic acid injection into the lateral brain ventricle in rat. *Acta Bioch Pol* 28: 111-122
11. Czuczwar SJ, Turski L, Turski W, Kleinrok Z (1981) Effects of some antiepileptic drugs in pentetrazol-induced convulsions in mice lesioned with kainic acid. *Epilepsia* 22: 407-414
12. Czuczwar SJ, Turski L, Kleinrok Z (1981) Diphenylhydantoin potentiates the protective effect of diazepam against pentylenetetrazol but not against bicuculline and isoniazid-induced seizures in mice. *Neuropharmacology* 20: 675-679
13. Czuczwar SJ, Turski L, Turski W, Kleinrok Z (1981) Effect of combined treatment of phenytoin with diazepam on the susceptibility of mice to electroconvulsions. *J Pharm Pharmacol* 33: 672-673
14. Turski L, Czuczwar SJ, Turski W, Kleinrok Z (1981) Studies of carbachol-induced wet-dog shake behaviour in rats. *Psychopharmacology* 73: 81-83
15. Turski L, Turski W, Czuczwar SJ, Kleinrok Z (1981) Evidence against the involvement of serotonergic mechanisms in wet dog shake behaviour induced by carbachol chloride in rats. *Psychopharmacology* 73: 376-380

16. Turski L, Czuczwar SJ, Turski W, Kleinrok Z (1981) Effect of antidepressant drugs on carbachol chloride-induced wet dog shake behaviour in rats. *Neuropharmacology* 20: 1193-1196
17. Turski L, Czuczwar SJ, Turski W, Kleinrok Z (1981) Effect of trazodone, mianserin, iprindole and zimelidine on wet dog shakes produced by carbachol in rats. *J Pharm Pharmacol* 33: 670-671
18. Turski L, Czuczwar SJ, Turski W, Kleinrok Z (1981) Shuttle behaviour in rats after lesion of hippocampal pyramidal cells with kainic acid. *Meth Find Exptl Clin Pharmacol* 3: 361-366
19. Turski W, Turski L, Czuczwar SJ, Kleinrok Z (1981) (RS)- α -Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid: Wet dog shakes, catalepsy and body temperature changes in rats. *Pharm Bioch Behav* 15: 546-549
20. Czuczwar SJ, Turski L, Kleinrok Z (1981) Effects of morphine, nalorphine and morphine withdrawal on lethal toxicity of intracerebroventricular kainic acid in mice. *Pol J Pharmacol Pharm* 33: 611-614
21. Turski L, Czuczwar SJ, Turski W, Kleinrok Z (1982) Induction of wet dog shakes by intracerebroventricular bethanechol in rats. Antagonism by neurotransmitter receptor blockers. *Pharmacology* 24: 105-110
22. Turski W, Czuczwar SJ, Turski L, Kleinrok Z (1982) The involvement of catecholaminergic mechanisms in the appearance of wet dog shakes produced by carbachol chloride in rats. *Arch int Pharmacodyn Ther* 255: 204-211
23. Turski L, Czuczwar SJ, Turski W, Sieklucka-Dziuba M, Kleinrok Z (1982) Diphenylhydantoin enhancement of diazepam effects on locomotor activity in mice. *Psycharmacology* 76: 198-200
24. Czuczwar SJ, Turski L, Kleinrok Z (1982) Effects of combined treatment with diphenylhydantoin and different benzodiazepines on pentylenetetrazol- and bicuculline-induced seizures in mice. *Neuropharmacology* 21: 563-567
25. Turski W, Czuczwar SJ, Turski L, Kleinrok Z (1982) Bilateral injection of kainic acid into the rat striatum potentiates morphine, arecoline and pilocarpine but not haloperidol catalepsy. *Meth Find Exptl Clin Pharmacol* 4: 287-291
26. Czuczwar SJ, Turski L, Turski W, Kleinrok Z (1982) Convulsant action of pentetrazol in rats with selective lesions of the hippocampal pyramidal cells with intracerebroventricular kainic acid. *Meth Find Exptl Clin Pharmacol* 4: 293-298
27. Turski L, Havemann U, Kuschinsky K (1982) Evidence for functional interactions of morphine in substantia nigra and striatum, in relation to muscular rigidity in rats. *Neurosci Lett* 28: 291-196
28. Turski L, Havemann U, Kuschinsky K (1982) Evidence that opioid receptors in the substantia nigra pars reticulata are relevant in regulating the function of striatal efferent pathways. *Behav Brain Res* 5: 415-422

29. Havemann U, Turski L, Kuschinsky K (1982) Role of gabaergic mechanisms in the substantia nigra pars reticulata in modulating morphine-induced muscular rigidity in rats. *Neurosci Lett* 31: 25-30
30. Turski W, Czuczwar SJ, Turski L, Kleinrok Z (1982) Effect of glutamic acid diethylester on (RS)- α -amino-3-hydroxy-5-ethyl-4-isoxazolepropionic acid- and kainic acid-induced changes of body temperature in rats. *Pol J Pharmacol Pharm* 34: 161-167
31. Czuczwar SJ, Turski L, Kleinrok Z (1982) Anticonvulsant action of phenobarbital, diazepam, carbamazepine, and diphenylhydantoin in the electroshock test in mice after lesion of hippocampal pyramidal cells with intracerebroventricular kainic acid. *Epilepsia* 23: 377-382
32. Havemann U, Turski L, Kuschinsky K (1982) Role of opioid receptors in the substantia nigra in morphine-induced muscular rigidity. *Life Sci* 31: 2319-2322
33. Turski L, Havemann U, Schwarz M, Kuschinsky K (1982) Disinhibition of nigral GABA output neurons mediates muscular rigidity elicited by striatal opioid receptor stimulation. *Life Sci* 31: 2327-2330
34. Turski L, Havemann U, Kuschinsky K (1982) On the possible role of excitatory amino acids in the striatum in mediating morphine-induced muscular rigidity. *Pharm Bioch Behav* 17: 715-719
35. Turski L, Schwarz M, Sontag K-H (1982) Interaction between phenytoin and diazepam in mutant Han-Wistar rats with progressive spastic paresis. *Naunyn-Schmiedeberg's Arch Pharmacol* 321: 48-51
36. Czuczwar SJ, Turski L, Kleinrok Z (1982) Diphenylhydantoin-induced potentiation of the anticonvulsant effect of diazepam against some types of experimental seizures. *Wiss Zeit Humboldt Univ (Berlin) Math-Nat R* 31: 493-494
37. Kleinrok Z, Turski L, Czuczwar SJ, Turski W (1982) Carbachol-induced wet dog shakes - A model for studying antidepressant drugs? *Wiss Zeit Humboldt Univ (Berlin) Math-Nat R* 31: 519-521
38. Turski WA, Cavalheiro EA, Turski L, Kleinrok Z (1983) Intrahippocampal bethanechol in rats: Behavioural, electroencephalographic and neuropathological correlates. *Behav Brain Res* 7: 361-370
39. Schwarz M, Turski L, Janiszewski W, Sontag K-H (1983) Is the muscle relaxant effect of diazepam in spastic mutant rats mediated through GABA-independent benzodiazepine receptors? *Neurosci Lett* 36: 175-180
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